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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/321,655	05/28/1999	STANTON L. GERSON	CWR-7091NP	6848

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EXAMINER

NGUYEN, QUANG

ART UNIT	PAPER NUMBER
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1633

MAIL DATE	DELIVERY MODE
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03/24/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/321,655	Applicant(s) GERSON, STANTON L.	
	Examiner QUANG NGUYEN, Ph.D.	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment filed on 12/28/2009 has been entered.

Claims 2-6 are pending in the present application, and they are examined on the merits herein.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the phrase “***human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation***” recited in new claim 6.

Response to Argument

Applicant's argument related to the above objection in the Amendment filed on 12/28/09 (page 8) has been fully considered but it is respectfully not found persuasive.

Applicant argues basically that the amended Application now provides a proper antecedent basis for the subject matter of claim 6.

It is noted that upon examination of the specifications of at least U.S. Patent Nos. 5,197,985 and 5,226,914, there is no written support for the concept that human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by simply adding the bone marrow specimen to a medium

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that contains factors which stimulate mesenchymal cell growth without differentiation as recited in claim 6.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons already set forth in the Office action mailed on 6/25/2009 (pages 3-4). ***The same rejection is restated below.***

Claim 6 recites the limitation “***human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation***”. In the amendment filed on 5/18/09, Applicants cited that the support for this new claim can be found in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584 which are incorporated by reference on page 5, lines 2-5 of the present application. Upon examination of page 5, lines 2-5 of the as-filed specification, there is no indication

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and/or suggestion that any of the U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584 has been incorporated by reference.

Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of invention as claimed at the time the application was filed.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 12/28/09 (pages 6-8) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicant argues basically that the amendment incorporating U.S. Patent Nos. 5,197,965 and 5,226,914 and PCT Publication No. WO 92/22584 by reference in their entirety is proper.

First, despite the incorporation by reference of U.S. Patent Nos. 5,197,965 and 5,226,914 and PCT Publication No. WO 92/22584, upon examination of the specifications of at least U.S. Patent Nos. 5,197,985 and 5,226,914, **there is no written support for the concept that human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by simply adding the bone marrow specimen to a medium that contains factors which stimulate mesenchymal cell growth without differentiation as recited in claim 6.** Both of the issued US patents teach that a bone marrow specimen (plugs of cancellous bone marrow) was added to a complete medium, vortexed, centrifuged,

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dissociated into single cells by passing complete medium containing the marrow cells through syringes fitted with a series of 16, 18, and 20 gauge needles and then **single cell suspension was plated in dishes for the purpose of selectively separating and/or isolating the marrow-derived mesenchymal cells** (col. 7, lines 22-52 in US 5,197,985; col. 6, line 53 continues to line 14 of col. 7 in US 5,226,914); **Or** aspirated bone marrow stem cells were added to the complete medium and fractionated with Percoll gradients, selecting the low density platelet fraction and then **plating the low density platelet fraction in the Petri dish for selective separation based upon cell adherence** (col. 7, line 53 continues to line 2 of col. 8 in US 5,197,985; col. 7, lines 15-32 in US 5,226,914). **Applicant also failed to point out the specific page and line numbers in any of the incorporated references that allegedly provide support for the limitation recited in claim 6.** Applicant is invited to do so.

Second, please note that “**Essential material**” may be incorporated by reference, **but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication**, which patent or patent application does not it self incorporate such essential material by reference. See 37 CFR 1.57 (c).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Nolta et al. (Blood 86:101-110, 1995, Cited previously) as evidenced by Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and/or (Mesenchymal stem cell-Wikipedia, the free encyclopedia, page 1-5, 2009) for the same reasons already set forth in the Office action mailed on 6/25/2009 (pages 5-6). ***The same rejection is restated below.***

Nolta et al. disclosed a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of a stroma generated by 4th passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells (Abstract, and column 1, page 102). The utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells (column 1, third paragraph, page 102), and it contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms “Mesenchymal stem cell” and “Marrow stromal cell” have been used interchangeably in the art as evidenced by Wikipedia, the free encyclopedia. Therefore, the bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolta et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue. With respect to new claim 6, the examiner interprets the

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limitation "human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation" is a product-by-process; and as such the isolated bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolte et al are indistinguishable from these mesenchymal stem cells for the reasons already outlined above. Additionally, please, also note that where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke*. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Nolte et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction by vigorous flushing and plating the collected cells twice to eliminate adherent stromal cells (column 1, last paragraph, page 102).

Accordingly, the method taught by Nolte et al meets every limitation of the claims as written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 12/28/09 (pages 10-17) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicant argues that Nolte et al do not discuss any mesenchymal stem cells. Even the bone marrow stromal cells at 4th passage of Nolte et al, which are devoid of most hematopoietic cells and contain some MSCs per Prockop, these stromal cells are not MSCs which have been isolated, purified and culturally expanded from human mesoderm tissue. In contrast to the irradiated stromal cells of Nolte et al, isolated, purified and culturally expanded human mesenchymal stem cells are multipotent and have the capacity to differentiate into more than one tissue type; and Nolte et al do not teach non-irradiated MSCs which have been isolated, purified and culturally expanded from a mesodermal tissue. Applicant also argue that the mesenchymal stem cells represent a well characterized isolated cell population which can be prepared in a reproducible manner in contrast to the heterologous stromal cell cultures described by Prockop which contain T and B lymphocytes, macrophages, dendritic cells and endothelial cells. Applicant also submits that Wikipedia is an invalid evidentiary reference and cannot properly be utilized in rejection of patent application claims. Finally, Applicant argues that the Examiner has provided no evidence in fact or technical reasoning that the bone marrow stromal cells of Nolte et al necessarily or inherently possess the characteristics of the presently claimed invention.

First, it is noted that the instant specification teaches specifically that human mesenchymal stem cells can be isolated and prepared according to any method known in the art, not necessarily limited only to the process of isolating, purifying, and expanding the marrow-derived mesenchymal stem cells in culture as described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584; and that the human mesenchymal stem cells can include a cell surface epitope specifically bound by antibodies from hybridoma cell line SH2, antibodies from hybridoma cell line SH2 **or** antibodies from hybridoma cell line SH4 (see at least page 5, first paragraph).

Second, as already set forth in the above rejection **the bone marrow stromal cell population** derived from bone marrow spicules **(after passage no. 4)** as taught by Nolta et al. **is devoid of most hematopoietic cells (column 1, third paragraph, page 102) and containing mesenchymal stem cells or multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop. Moreover, the terms “Mesenchymal stem cell” and “Marrow stromal cell” have been used interchangeably in the art** as evidenced by Wikipedia, the free encyclopedia. **By passaging bone marrow stromal cells and collected adherent bone marrow stromal cells at the 4th passage for transfection, Nolta et al in fact isolated, purified and culturally expanded bone marrow stromal cells or mesenchymal stem cells relative at least to collected bone marrow specimens and/or primary bone marrow stromal cell culture.** Human bone marrow is a human mesodermal tissue.

Third, the claims do not require any particular degree of purification/isolation and/or the human mesenchymal stem cells have to possess any particular set of cellular markers. Moreover, the claims also do not recite any particular isolation, purifying method step in the method as claimed.

Fourth, the above rejection has relied at least on the teachings of Prockop and/or the definition of the term “Mesenchymal stem cell” from Wikipedia as evidence why the the 4th passaged human bone marrow stromal cells of Nolta et al. contain human mesenchymal stem cells. It is noted that these bone marrow stromal cells of Nolta et al. were only irradiated a day prior to their use in the transduction of human CD34+hematopoietic progenitor cells. Moreover, Applicant also teaches explicitly that the mesenchymal stem cells may be irradiated prior to use in order to minimize or eliminate transduction of the mesenchymal stem cells (see page 6, lines 9-10). Additionally, the instant specification states explicitly “**Dexter stroma, in addition to MSCs**, contains T and B lymphocytes, macrophages, dendritic cells and endothelial cells” (page 2, lines 7-8). Since primary Dexter stroma already contained MSCs, then **selected adherent human bone marrow stromal cell population that is taught by Nolta et al also contains enriched MSCs because it is depleted of hematopoietic cells**. Furthermore, the instant specification states specifically “These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**” (page 13, lines 23-26)., and that **Dexter**

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stroma was derived from adhered bone marrow mononuclear cells that were passaged once (page 10, lines 12-23). These statements indicate clearly that **a much less purified, much more heterologous Dexter stromal cells (passaged only once) was already shown to be at least functionally equivalent to hMSCs used in the present invention**, let alone for the 4th passaged human allogeneic bone marrow stromal cells devoid of most hematopoietic cells taught by Nolte et al.

Fifth, there is no factual evidence of record indicating that the definition of the term “mesenchymal stem cell” from Wikipedia **is not acceptable** to an ordinary skilled in the art. Prockop et al (US 2002/0168765) stated, “Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and **“Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages”** (see the abstract). Prockop et al (US 2002/0168765) also taught clearly that **a given mesenchymal stem cell population is far from being homogeneous** (see at least paragraphs 9-18). This is also supported by Sylvester et al (US 7,592,174) who stated, “Despite the definitions ascribed to MSC populations by their in vitro differentiation capabilities, the mechanisms governing their proliferation and multi-lineage differentiation capacity have been poorly understood...**One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations**...This heterogeneity may be explained by the hypothesis that **true “mesenchymal stem cells” (cells with the ability to self-renew and differentiate**

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into multiple lineages) are only a small sub-population of the pool of cells termed MSCs, and the remainder of the mixed population consists of cells at various stages of differentiation and commitment....There are no universally accepted antigenic determinants of MSC" (col. 1, line 40 continues to line 16 of col. 2).

Accordingly, claims 3-6 are still rejected under 35 U.S.C. 102(b) for the reasons set forth above.

Claims 2 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Wells et al. (Gene therapy 2:512-520, 1995) as evidenced by Prockop, D.J. (Science 276:71-74; Cited previously) and/or (Mesenchymal stem cell-Wikipedia, the free encyclopedia, page 1-5, 2009) for the same reasons already set forth in the Office action mailed on 6/25/2009 (pages 9-11). ***The same rejection is restated below.***

Wells et al. disclosed a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with a retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of an autologous bone marrow stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5 (see at least Abstract and Materials and Methods, particularly pages 518-519). The utilized bone marrow stromal support contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the

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characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as evidenced by Wikipedia, the free encyclopedia. Therefore, the bone marrow stromal cells that were obtained between passages 3 and 5 for transduction as taught by Wells et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue. With respect to new claim 6, the examiner interprets the limitation "human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation" is a product-by-process; and as such the isolated bone marrow stromal cells that were obtained between passages 3 and 5 for transduction as taught by Wells et al are indistinguishable from these mesenchymal stem cells for the reasons already outlined above. Additionally, please, also note that where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton,

and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Wells et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction (column 1, first full paragraph, page 519).

Accordingly, the method taught by Wells et al meets every limitation of the claims as written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 12/28/09 (pages 17-23) have been fully considered but they are respectfully not found persuasive.

It is noted that Applicant presented the same arguments as those presented for the rejection of claims 3-6 as being anticipated by Nolta et al. (Blood 86:101-110, 1995, Cited previously) as evidenced by Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and/or (Mesenchymal stem cell-Wikipedia, the free encyclopedia, page 1-5, 2009). Basically, neither Wells et al nor Nolta et al teach the use of MSCs isolated, purified and culturally expanded from a mesodermic tissue.

Please refer to Examiner's responses to Applicant's same lines of arguments for the rejection of claims 3-6 above.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Qasba et al (US 6,225,119), filed on 05/21/1999, stated "The hematopoietic stem cells may be genetically modified (transduced or transformed or transfected) in the presence of the human mesenchymal stem cells, wherein the mesenchymal stem cells increase the efficiency of gene transduction of the hematopoietic stem cells" (col. 5, lines 58-62). However, this specific concept was not disclosed in the provisional application No. 60/086,420, filed on May 22, 1998, which is claimed as a priority document by US 6,225,119.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633